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Updates in Mechanical Thrombectomy

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Abstract

Strokes are a major source of morbidity and mortality worldwide. The long-standing gold standard in stroke therapy, intravenous administration of tissue plasminogen activator (tPA), is limited by strict timing parameters and modest efficacy in large strokes caused by thrombi in the proximal cerebral vasculature. Multiple recent randomized controlled trials have demonstrated the efficacy of mechanical thrombectomy for patients with large vessel occlusions (LVOs). Recent clinical guidelines have been updated to include mechanical thrombectomy as a standard of care in properly selected stroke patients, with ongoing and future studies working to refine the optimal clinical and technical variables of this approach.

Keywords: mechanical thrombectomy, large vessel occlusion, stroke, stent-retriever, endovascular

1. Large vessel ischemic stroke: an opportunity for improvement

Strokes are the third leading cause of death globally and the leading cause of acquired adult disability [1, 2]. There are approximately 700,000 strokes annually in the United States and 4.5 million stroke survivors suffering from disability and loss of independence [3]. Proximal large vessel occlusions (LVOs) are particularly devastating, with an approximate 60–80% risk of 90-day mortality or severe morbidity [4, 5]. Costs associated with the treatment of stroke patients are more than 22 billion dollars annually [3, 6]. With an aging global population, the incidence of stroke is expected to increase over time, making improvements in detection, treatment, and management essential.

The pathophysiology of ischemic strokes, which accounts for 85–90% of all strokes, is an ischemic cascade in the cerebral vasculature that leads to cellular bioenergetic failure. This injury is caused by cerebral hypoperfusion and subsequent excitotoxicity, oxidative stress, blood-brain barrier dysfunction, and post-ischemic inflammation that culminate in the death of neurons, glia, and endothelial cells [2]. Therapies targeting these deleterious pathways have been shown to improve cerebral perfusion and decrease secondary injury [7, 8], although rapid restoration of blood flow to affected areas remains the ultimate goal in stroke treatment.

Evidence-based indications (all criteria met)
Pre-stroke mRS 0–1
Acute ischemic stroke of ICA or proximal MCA receiving tPA within 4.5 hours
Age ≥ 18 years
NIHSS/ASPECTS ≥ 6
Thrombectomy initiated within 6 hours of symptom onset
Thrombectomy may be considered (no definitive data and imaging to determine infarct core/penumbra may be helpful)
>6 hours from symptom onset
Patients with contraindications to tPA
Distal MCA, ACA, and posterior circulation occlusions
<18 years of age
Pre-stroke mRS > 1, NIHSS/ASPECTS < 6
Abbreviations: ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT score; ICA, internal cerebral artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

Table 1. Summary of current indications for mechanical thrombectomy for stroke.

The long-standing gold standard for restoration of blood flow to ischemic brain is intravenous administration of the thrombolytic agent tissue plasminogen activator (tPA) within 3–4.5 hours of symptom onset [9, 10]. Tissue plasminogen activator leads to a 30% decreased risk of having no or minimal disability at 30 days [11]. However, strict parameters for tPA administration, such as its narrow treatment window and requirement that the patient has no recent surgeries, recent stroke, or prior hemorrhagic stroke, leave tPA underutilized. Only 3–5% of all stroke patients receive tPA, and less than half of patients that would be eligible for tPA actually receive treatment [12]. tPA is also associated with a 6% rate of hemorrhagic strokes and a 2% risk of systemic hemorrhage [13]. Most importantly, in high-risk patients with LVO, tPA has only modest rates of early reperfusion and thus limited efficacy [4, 5, 14, 15]. The limitations and risks of medical stroke therapies, particularly in patients with LVO, have led to the exploration of other reperfusion techniques by mechanical clot removal (thrombectomy). Recently, multiple large randomized trials demonstrated improved outcomes in patients with LVO [5, 16–19]. Based on this data, mechanical thrombectomy is now a standard of care in appropri-

ately selected stroke patients with LVO (**Table 1**) [20]. This chapter focuses on the theory, technical aspects, current data, and future directions of mechanical thrombectomy for stroke.

2. Introduction to mechanical thrombectomy

Mechanical thrombectomy employs direct arterial access to physically remove a thrombus from the cerebral circulation, providing in theory immediate and definitive reversal of hypoperfusion. While intuitively appealing, optimizing the technical aspects of this approach has delayed its widespread implementation. Early-generation devices included the MERCI Retriever (Concentric Medical Inc/Stryker Corp., Kalamazoo, MI), a flexible helical nitinol wire that is deployed through a microcatheter into the clot under balloon vessel occlusion and large-bore direct aspiration catheters with or without mechanical clot separators (Penumbra, Inc., Alameda, CA). Intra-arterial application of tPA directly to the site of the lesion was also explored in parallel to the above early techniques.

Initial randomized clinical trials with these devices/techniques demonstrated their safety but failed to show their superiority to intravenous tPA [4, 21, 22]. Potential reasons for the non-superiority of endovascular interventions in these trials include prolonged durations between symptom onset and intervention, poor patient selection as LVO was not in the selection criteria, and suboptimal recanalization rates likely resulting from use of early generation thrombectomy devices.

Newer generation stent retrievers, such as Solitaire FR (Covidien, Ltd., Mansfield, OH) and TREVO (Stryker Corp.), act as stents that are deployed within the clot and then retrieved to complete the thrombectomy. These devices have demonstrated superiority to older products like MERCI [23, 24] and are associated with significantly reduced endothelial damage [25]. Multiple large randomized trials have recently been published demonstrating improved outcomes in patients with LVO treated with stent retrievers as compared to intravenous tPA [5, 16–19], with clinical guideline updates including these therapies as standard of care.

3. Updated clinical data on mechanical thrombectomy

The American Heart Association (AHA)/American Stroke Association (ASA) released a set of updated guidelines for the management of patients with acute ischemic disease regarding endovascular treatment in 2015 after recent randomized controlled trial data clearly demonstrated the safety and efficacy of mechanical thrombectomy as compared to tPA for large vessel occlusion [20]. A summary of this clinical data follows and is highlighted in **Table 2**.

The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) enrolled 500 patients with anterior cerebral circulation arterial occlusion and an National Institutes of Health Stroke Scale (NIHSS) score ≥ 2 , who could

be treated endovascularly within 6 hours of symptom onset [5]. The effects of intra-arterial treatment plus standard medical therapy (intervention) versus standard medical therapy alone (control; including intravenous tPA, if eligible) were assessed. Mechanical thrombectomy was performed in 195 of 233 patients randomized to the intervention group, with retrievable stents used in 190 of these 195 patients. A modified thrombolysis in cerebral infarction (TICI) score of 2b or 3 (indicating >50% or complete distal reperfusion, respectively) was achieved in 58.7% of patients in the intervention group. This study reported a 13.5% increase in functional independence in the intervention group (32.6 versus 19.1, $p < 0.05$ as determined by the primary study outcome 90-day modified Rankin Scale [mRS] ≤ 2), with no significant difference in mortality or intracerebral hemorrhage rates. Secondary outcomes of the 5- and 7-day NIHSS score, the absence of residual occlusion at 24 hours, and the infarct volume were also improved in the intervention group.

The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial enrolled 316 patients with proximal anterior circulation occlusions, moderate-to-good collateral circulation, and a small infarct core, up to 12 hours after symptom onset [16]. The effects of intra-arterial treatment plus standard medical therapy (intervention) versus standard medical therapy alone (control; including intravenous tPA, if eligible) were assessed. This study was terminated early after an interim analysis demonstrated clear treatment efficacy. One hundred and fifty-one of the 165 patients assigned to the intervention group received intra-arterial therapy, with retrievable stents used in 130 of these patients. A modified TICI 2b or 3 score was achieved in 72.4% of patients in the intervention group. This study reported a 23.7% increase in functional independence (90-day mRS ≤ 2) with intervention (53.0 versus 29.3%, $p < 0.05$; a primary study outcome) and a decrease in 90-day mortality (10.4 versus 19.0%; $p = 0.04$). Secondary quality of life outcomes including 90-day Barthel Index (BI), NIHSS, and EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) all favored the intervention group as well.

The Solitaire FR with the Intention for Thrombectomy as Primary Endovascular Treatment of Acute Ischemic Stroke (SWIFT PRIME) trial enrolled 196 patients with confirmed proximal anterior circulation occlusions and the absence of a large ischemic core that could be treated within 6 hours of symptom onset [17]. The effects of intravenous tPA (control) versus intravenous tPA plus stent-retriever thrombectomy (intervention) were assessed. This study was terminated early after an interim analysis demonstrated clear treatment efficacy. The intervention group of 98 patients had a median time from qualifying imaging to groin puncture of 57 minutes. At the end of the procedure, the rate of substantial reperfusion was 88%. This study reported a 25% increase in functional independence (90-day mRS ≤ 2) with intervention (60 versus 35%, $p < 0.001$; a primary study outcome). Secondary outcomes including 27-hour successful reperfusion and NIHSS were also significantly improved in the intervention group. There were no significant differences between the intervention and control group in 90-day mortality or symptomatic intracranial hemorrhage.

Trial name	Year	Study design	Groups	Number of patients	Study criteria	Interventional outcome	Clinical outcome	Reference
Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)	2015	Rando- mized, contr- olled	Intra-arterial treatment + usual care versus usual care alone	500 (233 treatment [81% stent retriever]; 267 control)	Proximal anterior circulation occlusions, NIHSS ≥ 2 , treated within 6 hours	58.7% TICI 2b or 3 score with intervention	13.5% increase in rate of functional independence (90-day mRS ≤ 2) with intra-arterial intervention (32.6 versus 19.1%; $p < 0.05$). No significant difference in mortality or symptomatic intracerebral hemorrhage	[5]
Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE)	2015	Rando- mized, contr- olled	Intra-arterial treatment + usual care versus usual care alone	316 (165 treatment [78% stent retriever]; 150 control)	Proximal anterior circulation, moderate-to-good collateral circulation, small infarct core, treated within 12 hours	72.4% TICI 2b or 3 score with intervention	23.7% increase in functional independence (90-day mRS ≤ 2) with intra-arterial intervention (53.0 versus 29.3%, $p < 0.05$) and a decrease in 90-day mortality (10.4 versus 19.0%; $p = 0.04$)	[16]
Solitaire FR With the Intention for Thrombectomy as Primary	2015	Rando- mized, contr- olled	Stent-retriever thrombectomy + usual care	196 (98 stent retriever; 98 control)	Proximal anterior circulation occlusions,	88% rate of substantial reperfusion	25% increase in functional independence (90-day mRS ≤ 2)	[17]

Trial name	Year	Study design	Groups	Number of patients	Study criteria	Interventional outcome	Clinical outcome	Reference
Endovascular Treatment of Acute Ischemic Stroke (SWIFT PRIME)			versus usual care alone		no large ischemic core, treated within 6 hours		with intervention (60 versus 35%, $p < 0.001$). No significant difference in 90-day mortality or symptomatic intracranial hemorrhage	
Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial (EXTEND-IA)	2015	Randomized, controlled	Stent-retriever thrombectomy + usual care versus usual care alone	70 (35 stent retriever; 35 control)	Proximal anterior circulation occlusions, no large ischemic core, treated within 6 hours	86% TICI 2b or 3 score with intervention	31% increase in functional independence (90-day mRS ≤ 2) with intervention (71 versus 40%; $p = 0.01$). No significant difference in 90-day mortality or symptomatic intracranial hemorrhage	[18]
Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT)	2015	Randomized, controlled	Stent-retriever thrombectomy + usual care versus usual care alone	206 (103 intervention [98 stent retriever]; 103 control)	Proximal anterior circulation occlusions, no large ischemic core, treated within 8 hours	65.7% TICI 2b or 3 score with intervention	15.5% increase in functional independence (90-day mRS ≤ 2) with intervention (43.7 versus 28.2%, $p < 0.05$). No significant difference in 90-	[19]

Trial name	Year	Study design	Groups	Number of patients	Study criteria	Interventional outcome	Clinical outcome	Reference
							day mortality or symptomatic intracranial hemorrhage	

Abbreviations: mRS, modified Rankin Scale; TICI, thrombolysis in cerebral infarction score.

Table 2. Summary of randomized controlled trials for mechanical thrombectomy in stroke.

The Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial (EXTEND-IA) trial was designed similarly to SWIFT PRIME and enrolled 70 patients with confirmed proximal anterior circulation occlusions and the absence of a large ischemic core that could be treated within 6 hours of symptom onset [18]. Again, the effects of intravenous tPA (control) versus intravenous tPA plus stent-retriever thrombectomy (intervention) were assessed, and this study was also terminated early after an interim analysis demonstrated clear treatment efficacy. The 35 patients in the intervention group had a median time from qualifying imaging to groin puncture of 93 minutes. A modified TICI 2b or 3 score was achieved in 86% of patients in the intervention group. This study reported a significant increase in ischemic territory reperfusion at 24 hours with intervention (median 100 versus 37%; $p < 0.001$) and increased neurologic improvement at 3 days (80 versus 37%; $p < 0.01$). They also report a 31% increase in functional independence (90-day mRS ≤ 2) with intervention (71 versus 40%; $p = 0.01$), with no significant difference in rate of symptomatic intracerebral hemorrhage or death.

The Endovascular Revascularization with Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke within 8 Hours (REVASCAT) trial enrolled 206 patients with occlusion of the proximal anterior circulation and the absence of a large ischemic core who could be treated within 8 hours of symptom onset [19]. The effects of stent-retriever thrombectomy plus standard medical therapy (intervention) versus standard medical therapy alone (control; including intravenous tPA, if eligible) were assessed. This study was terminated early after an interim analysis demonstrated clear treatment efficacy. Ninety-eight of the 103 patients in the intervention group underwent thrombectomy, with a median time from stroke onset to groin puncture of 269 minutes. A modified TICI 2b or 3 score was achieved in 65.7% of patients in the intervention group. This study reported a 15.5% increase in functional independence (90-day mRS ≤ 2) with intervention (43.7 versus 28.2%, $p < 0.05$; a primary study outcome). Secondary functional outcomes including 90-day BI, NIHSS, and EQ-5D all favored the intervention group, as did the median 24-hour infarct volume. There were no significant differences between the intervention and control groups in 90-day mortality or symptomatic intracranial hemorrhage.

These five trials clearly demonstrate the therapeutic efficacy of mechanical thrombectomy with stent retrievers in stroke patients with LVO. The dramatic results from these studies (with

multiple trials being stopped early for treatment efficacy) demanded a rapid update of clinical guidelines.

4. Updates of stroke treatment guidelines: role of mechanical thrombectomy

In response to the above trials and other recent smaller studies, in 2015 the American Heart Association (AHA) and American Stroke Association (ASA) released a focused update of the 2013 guidelines for the endovascular treatment of patients presenting with acute ischemic stroke [20].

These updated guidelines fall under several classifications of recommendation and levels of evidence. Class I recommendations imply that the benefits of the suggested procedure well outweighs the potential risks, and therefore indicate that the treatment should be administered. Class IIa recommendations indicate a moderate outweighing of benefit over risk and suggest that a treatment is reasonable to consider performing, but further studies are needed to ensure appropriate clinical application. Class IIb recommendations indicate that the benefits of the procedure may or may not outweigh its associated risks, and these procedures may be considered, although higher classifications of treatment recommendations take priority. Evidence pertaining to individual recommendations is stratified by level, indicating the strength of supporting data. Level A indicates that multiple populations have been evaluated and that data supporting the recommendation has been derived from multiple trials. Level B indicates that fewer populations have been evaluated or that the data supporting the recommendation has been derived from a single trial. Level C data indicates that the only data supporting the recommendation are the opinions of experts, case studies, or current standard of care [26].

A summary of the AHA/ASA 2015 guidelines detailing recommendations for treatment of patients using mechanical thrombectomy is as follows [20]. If patients meet all of the following criteria, mechanical thrombectomy using stent retriever is indicated and should be performed (Class I, Level of Evidence A): (a) prestroke mRS (modified Rankin Scale) score of 0 or 1, (b) presentation of acute ischemic stroke and receiving intravenous tPA within 4.5 hours of symptom onset, (c) causative occlusion of internal carotid artery or proximal MCA (M1), (d) age of at least 18 years, (e) NIHSS score of at least 6, (f) Alberta Stroke Program Early CT score (ASPECTS) of at least 6, and (g) treatment that can be initiated within 6 hours of symptom onset.

Importantly, eligible patients should receive tPA even if endovascular treatments are being considered, and contrary to previous guidelines, observation of patients after administration of tPA for clinical response is no longer required nor recommended prior to initiation of endovascular treatment (Class III, Level of Evidence B [randomized data]). Additionally, the ASA states that the use of stent retrievers is preferable to the MERCI device (Class I, Level of Evidence A) and that the use of alternate mechanical thrombectomy devices aside from stent retrievers may be acceptable in some cases (Class IIb, Level of Evidence B [non-randomized data]) [20].

The new guidelines have also stipulated that the ultimate goal of mechanical thrombectomy should be a modified TICI score of 2b/3 in angiographic imaging (Class I, Level of Evidence A), as early as possible and within 6 hours of stroke onset (Class I, Level of Evidence B [randomized]) [20]. If mechanical thrombectomy following intravenous tPA administration is not adequate to achieve this angiographic result, the use of additional adjuncts including intra-arterial fibrinolysis is indicated to maximize the angiographic result (Class IIb, Level of Evidence B [randomized]). The treatment efficacy of mechanical thrombectomy initiated longer than 6 hours from symptom onset is unknown; however, additional trials are needed to determine the clinical benefit in this setting [20].

While adhering to the above recommendations is ideal for maximal clinical benefit, acute ischemic stroke patients are heterogeneous. The ASA thus included alternate recommendations for patient subpopulations/clinical situations not covered above. These expanded recommendations are as follows [20]. The use of stent retrievers alone is reasonable in patients presenting with anterior circulation occlusion even when intravenous tPA is contraindicated (i.e., outside of time window, prior stroke, head trauma, hemorrhagic coagulopathy, etc.) (Class IIa, Level of Evidence C). However, there is currently inadequate data definitively determining the clinical efficacy of monotherapy alone for this patient cohort. Intra-arterial fibrinolysis may be considered in these patients, but the clinical benefit of this approach has also yet to be established (Class IIb, Level of Evidence C).

Although no study-based evidence exists, the ASA recommendations include the use of stent retrievers in patients experiencing causative occlusions of the M2 or M3 portions of the MCA, anterior cerebral artery, vertebral arteries, basilar arteries, and posterior cerebral arteries, if treatment can be initiated within 6 hours of symptom onset (Class IIa, Level of Evidence C). Stent retrievers may also be appropriate in treatment of patients under 18 years of age with occlusion of large vessels and patients with an mRS score of >1, an ASPECTS score <6, or an NIHSS score <6 who present with causative occlusions of the internal carotid artery or proximal MCA (M1) (Class IIb, Level of Evidence C). However, randomized trials are required to provide data on the clinical efficacy of stent-retriever usage in such patients.

Additionally, the updated guidelines discuss multiple technical aspects of endovascular intervention in strokes [20]. Specifically, they state the use of a proximal balloon guide catheter or a large-bore distal access catheter to provide flow stasis, and/or simultaneous aspiration as opposed to a cervical guide catheter alone during stent-retriever thrombectomy may be beneficial (Class IIa, Level of Evidence C). Future studies are nonetheless needed to determine the optimal technical approach with regard to recanalization and distal embolization rates. They also state that angioplasty and stenting of proximal cervical atherosclerotic stenoses or occlusions at the time of thrombectomy are reasonable (Class IIb, Level of Evidence C), although the utility of this intervention is currently unknown.

Lastly, the guidelines addressed the issue of conscious sedations versus general anesthesia during mechanical thrombectomy. However, given a lack of randomized trial data, they state that anesthetic selection should be patient-based after considering individual risk factors, tolerance of procedure, other clinical characteristics, and evaluation of a patient's medical history [20].

5. Future considerations in mechanical thrombectomy

Despite being the new gold standard for large vessel acute stroke, there remain multiple unknown technical and clinical variables regarding the optimization of mechanical thrombectomy for strokes. As alluded to in the above guideline summary, outstanding clinical questions requiring further study include the use of adjunct imaging modalities to further define an acceptable pre-intervention ischemic core/penumbra (e.g., CT-perfusion/diffusion and perfusion-weighted imaging), the utility of simultaneous lesional catheter aspiration versus standard carotid balloon occlusion, the efficacy of thrombectomy in the posterior circulation, and the maximal acceptable timing of intervention from symptom onset.

Moreover, many technical aspects of the devices employed are still being optimized. Future device designs will center on reduction of the endothelial footprint both by changing device design and optimizing device size relative to the vasculature. Additionally, reduction of embolic complications beyond those afforded by direct lesional aspiration, and increasing first pass success, will be major driving forces behind future iterations of stent-retriever devices.

Guiding these changes is a fundamental inquiry into stroke physiology, and how device characteristics beyond efficacy of clot removal can affect outcomes. For example, an area of ongoing and future study is the potential role of iatrogenic endothelial damage on post-thrombectomy secondary neurologic injury (**Figure 1**). The potential importance of endothelial injury becomes apparent upon close analysis of existing clinical data. Specifically, while the initial equivocal thrombectomy clinical trial data is likely due in part to lower recanalization rates than with more recent studies [4, 5, 16–19, 21, 22], another potential explanation may relate to the increased iatrogenic endothelial injury generated by older thrombectomy devices when studied in both in vitro and in vivo models [25]. When combined with the known deleterious effects of physiologic blood flow disruptions on endothelial cell homeostasis and cytokine signaling [27–37], these findings necessitate future studies to determine how iatrogenic endothelial damage affects secondary neuronal injury in post-thrombectomy stroke patients. This line of study is critical to next generation device design.

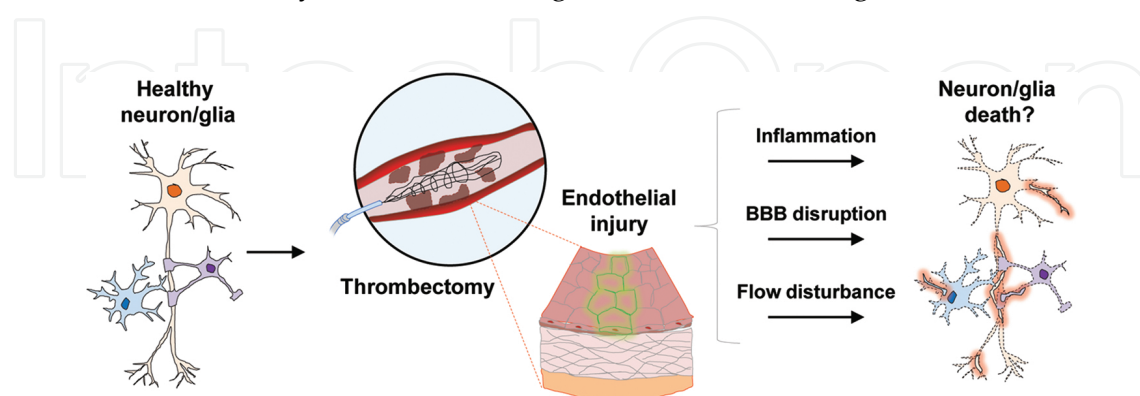


Figure 1. Schematic illustration of the potential negative effects of iatrogenic endothelial damage during thrombectomy on downstream neurons/glia. Proposed deleterious mechanisms include upregulation of inflammatory pathways, blood-brain barrier (BBB) disruption, and flow disturbances. Ongoing work to understand these effects will inform future thrombectomy device design.

In summary, mechanical thrombectomy for selected patients with large vessel acute stroke is the new standard of care based on overwhelming clinical efficacy data. Future studies and technical and procedural refinements will undoubtedly increase the indications for this intervention.

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